Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 35, 37-43 and 45 are pending in the application, with claims 35 and 43 being the independent claims. Claims 36, 44 and 46-52 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 35 and 43 are sought to be amended. No new matter is added by way of these amendments. It is believed that the amendments presented above will place the application in condition for allowance and/or in better form for appeal. *See* 37 C.F.R. § 1.116(a). It is respectfully requested that the amendments after final Office Action be entered and considered.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Election/Restrictions

Applicants wish to thank the examiner for rejoining claims 43-45 with claims 35-42 of Group I, the elected invention.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 35-45 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. *See* Office Action, page 2. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention. *See id.* Applicants respectfully traverse this rejection.

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). As discussed below, Applicants submit that a person of ordinary skill in the art would have been able to practice the methods of the present claims without undue experimentation. Applicants also submit that the reasons for the rejection, as set forth in the Office Action, are insufficient to establish a *prima facie* case of non-enablement.

The specification teaches exemplary modes of formulation and administration of antisense oligonucleotides and ribozymes for use in the practice of the claimed methods. *See* specification at page 30, lines 21-27. The specification also teaches various routes of administration that can be used in the context of the present invention such as, *e.g.*, parenteral, subcutaneous, intravenous, intramuscular, intra-peritoneal, transdermal, intrathecal or intracranial. *See* specification at page 31, lines 1-3. Moreover, the

specification recites various factors to be considered in determining the appropriate dosage of antisense oligonucleotides and ribozymes that are administered in the practice of the claimed methods. According to the specification:

> The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. For example, as much as 700 milligrams of antisense oligonucleotide has been administered intravenously to a patient over a course of 10 days (i.e., 0.05 mg/kg/hour) without signs of toxicity (Sterling, "Systemic Antisense Treatment Reported," *Genetic Engineering News 12(12)*:1, 28 (1992)).

Specification at page 31, lines 3-9.

Furthermore, the knowledge in the art regarding the administration of antisense oligonucleotides and ribozymes for therapeutic purposes, in view of the present specification, would have provided additional guidance for the practice of the claimed methods. As noted in Applicants' previous response, there are many examples from the scientific literature that demonstrate successful therapeutic applications of antisense oligonucleotides. *See* Applicants' Amendment and Reply Under 37 C.F.R. § 1.111, filed November 7, 2003 ("the November 7, 2003 response"), at page 12; *see also* Galderisi *et al., J. Cell Physiol. 181*:251-257 (1999) (submitted as Exhibit A with the November 7, 2003 response). These examples would have supplemented the teachings of the present specification and would have provided additional guidance to those of ordinary skill in the art in practicing the currently claimed methods.

In view of the teachings in the specification and the knowledge generally available in the art at the time of the effective filing date of the present application, a

person of ordinary skill would have been able to practice the full scope of methods encompassed by the present claims without undue experimentation.

The Examiner has not set forth a reasonable basis to question the enablement provided for the claimed invention and therefore has not established a *prima facie* case of non-enablement. The Examiner stated that the specification:

> does not provide guidance or examples that would show by correlation what sequences of antisense based nucleic acid compounds of the method would predictably provide for treatment or prevention of disease in general or for the treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas specifically.

Office Action, page 3. Applicants respectfully disagree. Independent claims 35 and 43 specify that the antisense oligonucleotide and ribozyme used in the practice of the claimed method, are complementary to an NTP mRNA sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1. In addition, the specification provides exemplary regions of SEQ ID NO:1 to which the antisense oligonucleotides and ribozymes of the invention may be complementary. *See* specification at page 25, lines 18-24. The specification also notes that oligonucleotide sequences which are non-homologous to pancreatic thread protein (PTP) are preferred. *See* specification at page 26, lines 1-6. A person of ordinary skill in the art, in view of the teachings in the specification and the general knowledge in the art regarding antisense therapies, would have been able to select appropriate nucleotide sequences to effectively interfere with the expression of AD7c-NTP in an animal using the claimed methods. *See also* the December 19, 2003 response at page 10. In addition, Applicants note that claim 38 specifies that the antisense oligonucleotide is selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10 and SEQ ID NO:11.

The Examiner also stated that "[t]he instant specification does not provide guidance or examples that would show by correlation what modes of delivery would predictable [sic] provide for a treatment of disease in general and for the treatment or prevention of neuroectodermal tumors, malignant astrocytomas and glioblastomas in particular." Office Action, pages 3-4. As noted in the November 7, 2003 response (page 11), a person of ordinary skill in the art would recognize that any mode of delivery that brings oligonucleotide-based therapeutic molecules into contact with neuronal cells in an animal would be effective in the context of the present invention. In addition, the specification describes various modes of administration that can be used in the practice of the invention. *See* specification at page 30, line 28, through page 31, line 3. The Examiner has not provided evidence or sound scientific reasoning to indicate that any one of these modes of administration would not be expected to work. The Examiner's statement quoted above is insufficient to support the rejection.

In explaining the rejection, the Examiner made several comments relating to the Galderisi reference, which Applicants cited in the November 7, 2003 response. The Examiner has pointed to various sentences from Galderisi that, when taken out of context, are asserted to support the contention that the use of antisense oligonucleotides is unpredictable. *See* Office action, page 9. For instance, the Examiner quoted the following sentence from the abstract of Galderisi: "The use of antisense to modify gene expression is variable in its efficacy and reliability..." In the sentences that immediately follow the one quoted by the Examiner, however, Galderisi describes how antisense oligonucleotides have been clinically successful:

> However, preliminary results of several clinical studies demonstrated the safety and to some extent the efficacy of

> antisense oligodeoxynucleotides (ODNs) in patients with malignant diseases. Clinical response was observed in some patients suffering from ovarian cancer who were treated with antisense targeted against the gene encoding for the protein kinase C-alpha. Some hematological diseases treated with antisense oligos targeted against the bcr/abl and the bcl2 mRNAs have shown promising clinical response. Antisense therapy has been useful in the treatment of cardiovascular disorders such as restenosis after angioplasty, vascular bypass graft occlusion, and transplant coronary vasculopathy. Antisense oligonucleotides also have shown promise as antiviral agents. Several investigators are performing trials with oligonucleotides targeted against the human immunodeficiency virus-1 (HIV-1) and hepatitis viruses. Phosphorothiotate ODNs now have reached phase I and II in clinical trials for the treatment of cancer and viral infections, so far demonstrating an acceptable safety and pharmacokinetic profile for continuing their development. The new drug Vitravene[1], based on a phosphorothioate oligonucleotide designed to inhibit the human cytomegalovirus (CMV), promises that *some substantial successes can be reached with the antisense technique.*

Galderisi, page 251, abstract, (emphasis added). Thus, Galderisi makes it clear that antisense oligonucleotide therapies have been successfully applied in clinical settings.

In view of the teachings in Galderisi, Applicants maintain their assertions that: (a) the general techniques that were used to produce positive clinical outcomes in the examples mentioned in Galderisi would have been available to persons of ordinary skill in the art at the time of the effective filing date of the present application; (b) the ability of others to successfully apply antisense techniques in the treatment of conditions such as cancer, hematological diseases and cardiovascular disorders strongly suggests that

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[1] Vitravene® is sold by Isis Pharmaceuticals, Inc. The Isis Pharmaceuticals website (http://www.isispharm.com/product_pipeline-P.html, last visited December 2, 2004) lists eleven antisense pharmaceutical products, in addition to Vitravene®, that are in the company's product pipeline. A copy of the Isis antisense product pipeline information, obtained from the website, is submitted herewith as Exhibit A.

antisense techniques could also have been successfully applied in the treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas; and (c) the Examiner has not provided sufficient evidence or sound scientific reasoning to rebut the presumption that Applicants' specification enables the practice of the claimed invention.

Applicants also maintain their position that the references cited at pages 4-7 of the Office Action to support the rejection (*i.e.*, Agrawal (1996), Branch (1998), and Jen and Gewirtz (2000)) do not indicate that the practice of the claimed invention would have required undue experimentation. Indeed, these references describe examples from the art of the successful use of oligonucleotide-based therapeutic molecules for the treatment of clinical disorders, and therefore support Applicants' position that the currently claimed invention is fully enabled. *See* the November 7, 2003 response at pages 13-17.

Since the present specification, in view of the teachings in the art, would have enabled a person of ordinary skill to practice the currently claimed methods without undue experimentation, and since no specific scientific evidence or reasoning has been presented to indicate otherwise, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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